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FPIN's Clinical Inquiries

Monitoring Therapy for Patients with Alzheimer's Disease

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Clinical Question

How do you monitor patients with Alzheimer's disease to determine if they are benefiting from receiving a cholinesterase inhibitor?

Evidence-Based Answer

Patients with Alzheimer's disease who undergo treatment of any kind should be monitored eight weeks after initiation of therapy and at least every six months thereafter. (Strength of Recommendation: C, based on expert opinion and extrapolation from drug effectiveness studies)

There are no clinical trials directly assessing the best way to monitor patients on a cholinesterase inhibitor. The Alzheimer's Disease Assessment Scale for Cognition (ADAS-Cog) and the Clinician Interview-Based Impression of Change Scale plus Caregiver Input (CIBICS-CI) are the most commonly used instruments to establish effectiveness of Alzheimer's medications in clinical trials; however, these tools are lengthy and cumbersome to use. The Mini-Mental State Examination (MMSE) also has been used in clinical trials of cholinesterase inhibitors, and although it is familiar to most physicians, it lacks specificity.

Evidence Summary

For a new Alzheimer's disease medication to receive U.S. Food and Drug Administration approval, clinical trials must show that it improves cognitive and global function according to a validated assessment scale.1 The ADAS-Cog, which evaluates language, orientation, motor skills (praxis), and memory, is the standard instrument for measuring cognitive function in clinical trials.2 It represents one of two subsets of the Alzheimer's Disease Assessment Scale. The maximal score possible is 70, with worsening dementia resulting in a higher score. Unfortunately, the ADAS-Cog is not an ideal test for use by primary care physicians because it requires training to administer it, and the test can take 30 to 45 minutes to complete.3

Untreated patients with Alzheimer's disease show a statistically significant increase of four to six points over 12 months on the ADAS-Cog, and persons without Alzheimer's disease show no significant change.2,4 Over the first six to 12 months, patients treated with cholinesterase inhibitors showed improvement by an average of 2.7 points.5 However, literature suggests that 30 to 50 percent of patients may not respond to treatment at all, and 20 percent may have better-than-average improvement.6

The CIBICS-CI is the assessment tool most commonly used to determine global functional change in drug trials.2,7 The Alzheimer's Disease Cooperative Study created a standardized version of this test, which consists of semi-structured interviews of the patient and a caregiver followed by an evaluation of change on a seven-point scale.

In one prospective trial, the CIBICS-CI was found to have good short-term reliability, with 94 percent of patients with Alzheimer's disease showing little or no change at one month. It was validated as demonstrating significant global decline in patients with Alzheimer's disease (56 percent of patients at six months and 81 percent at 12 months) and no significant change in patients in a control group over the same period.8 Most physicians are not familiar with the CIBICS-CI, and the interviews typically take a minimum of 40 minutes to perform.

Although initially designed as a screening tool, many clinical trials have used the MMSE as a secondary measure of cognitive function because most physicians are familiar with it and because it is easy to administer, usually taking 5 to 10 minutes to complete. The MMSE consists of 30 items that evaluate orientation, memory, attention, language, and motor skills.

Untreated patients with Alzheimer's disease usually decline two to four points per year on the MMSE.2 The MMSE shows good internal consistency and good test-retest reliability. Most studies reveal the MMSE has a sensitivity and specificity between 80 to 100 percent in detecting dementia9,10; however, it has increased variability compared with the ADAS-Cog and is not considered specific enough to be used alone to evaluate treatment response.2,5 The MMSE also becomes less sensitive to progressive decline as the lower limits of the scale are approached.10

Of the many assessment tools validated for use in patients with Alzheimer's disease, there are several that demonstrate the effectiveness of cholinesterase inhibitors versus placebo in randomized controlled trials (Table 111,12). Other scales that have the potential to be useful include the Instrumental Activities of Daily Living Scale, Geriatric Depression Scale, and Caregiver Burden Scale.12

Table 1. Tools Detecting Positive Outcomes in Patients with Alzheimer's Disease on Cholinesterase Inhibitors

Measurement	Tool
Cognitive function	Alzheimer's Disease Assessment Scale for Cognition; Mini-Mental State Examination*
Clinical Global Impression or Global Disease Severity	Clinical Dementia Rating Scale†; Clinician Interview-Based Impression of Change Scale plus Caregiver Input; Gottfries, Brane and Steen Scale†; Mental Function Impairment Scale†
Activities of daily	Caregiver-rated Modified Crichton Scale†; Disability

living	Assessment for Dementia; Progressive Deterioration Scale; Instrumental Activities of Daily Living Scale*†; Physical Self-Maintenance Scale†
Behavioral disturbances or quality-of-life	Neuropsychiatric Inventory Questionnaire*

*- Recommended by the American Family Physician review article.

†- Used in donepezil (Aricept) trials only.

Information from references 11 and 12

Recommendations from Others

No subspecialty group guidelines give concrete recommendations regarding how monitoring should be done or which tools should be used. The Alzheimer's Association suggests postdiagnostic monitoring of patients every six months or any time there is a behavioral change or sudden decline in function.13

Clinical Commentary

Monitoring the clinical effect of a cholinesterase inhibitor is difficult because of the varying symptoms and rate of decline among patients with Alzheimer's disease. The CIBICS-CI and other global function scales were designed to measure clinically meaningful and distinct changes2; however, these scales are cumbersome to administer in the outpatient setting. Assessment of meaningful change could perhaps be tailored to each patient by using shorter tests or clinical interview questions that document improvement or stability in the one or more domains most troublesome to a specific patient and his or her family.

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Clinical Inquiries provides answers to questions submitted by practicing family physicians to the Family Physicians Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review. The strength of recommendations and the level of evidence for individual studies are rated using criteria developed by the Evidence-Based Medicine Working Group (http://www.cebm.net/levels_of_evidence.asp).